

## **REMARKS**

### **I. Status of Claims**

Claims 14, 15, 18, 19, 22 and 23 have been cancelled (without prejudice or disclaimer and retaining the right to represent in a subsequent divisional or continuing application) as being directed to unelected subject matter. Claims 6 and 11 have been cancelled without prejudice or disclaimer and retaining the right to represent in a subsequent divisional or continuing application. Claims 1, 3, 4, 10, 12, 13 and 20 have been amended.

Claim 1 has been amended to incorporate the language found in now cancelled claim 6. Claim 1 has been amended to add the term “covalently”. Support for this amendment comes from the specification as filed at pages 13-15 in Schemes 1-4 and at pages 19-27 in Examples 1-8.

Claims 3 and 4 have been amended to add “of said block polymer” for clarity.

Claims 10 and 20 have been amended to delete “its main component”, replacing it with “an active ingredient”. Support for this amendment comes from the specification as filed at page 5, lines 12-35 and page 6, lines 1-22.

Claim 12 has been amended to depend from claim 1 and to incorporate the language in now cancelled claim 11.

Claim 13 has been amended to replace the phrase “in the form of an injection” with the phrase “in the form suitable to be filled in a syringe”. Support for this amendment comes from the specification as filed at page 18, lines 17-18. Claim 13 has been further amended to now depend from claim 12.

No new matter has been added.

Claims 1-5, 7-10, 12, 13, 16, 17, 20 and 21 are pending.

## **II. Claim Rejections**

### **a) 35 U.S.C. § 112, Second Paragraph**

Claims 1-13, 16, 17, 20 and 21 stand rejected as being indefinite. Applicants respectfully traverse.

The Examiner contends that claim 1 is indefinite because it is unclear from the claim language or from the specification whether the claim requires that the hyaluronic acid be covalently bound or non-covalently associated with the block polymer. Without conceding the correctness of the Examiner's position or the need for amendment, claim 1 has been amended to add the phrase "covalently" to define that the hyaluronic acid is covalently bound to the block polymer. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner contends that claims 3 and 4 are indefinite because it is not clear from the claims or specification whether the limitation "at only one of its two ends" applies to the hyaluronic acid polymer or the block polymer. Without conceding the correctness of the Examiner's position or the need for amendment, claims 3 and 4 have been amended to add the phrase "of said block polymer" after the phrase "at only one of its two ends." Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner also contends that claim 10 (and also claim 20) are indefinite because it is unclear from the claims and the specification whether the phrase "main component" is intended to

mean the component present in the largest amount or the active ingredient. Without conceding the correctness of the Examiner's position or the need for amendment, claims 10 and 20 have been amended to delete the phrase "as its main component" replacing it with the phrase "as an active ingredient." Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner also contends that claim 13 is indefinite because it is not clear from the claims or the specification whether this limitation refers to any composition that could conceivably be safely injected into a subject, or only to those actually introduced with a hypodermic syringe or other apparatus for injection. Without conceding the correctness of the Examiner's position or the need for amendment, claim 13 has been amended to replace the phrase "in the form of injection" with the phrase "in the form suitable to be filled in a syringe." Reconsideration and withdrawal of this rejection is respectfully requested.

**b) 35 U.S.C. § 112, First Paragraph**

Claims 11 and 13 have been rejected as not being enabled. The Examiner contends that the specification, while being enabling for a pharmaceutical preparation for treating the specific cartilage disorders recited in claim 12, does not reasonably provide enablement for a method of treating any joint disease. Applicants respectfully traverse. Without conceding the correctness of the Examiner's position, claim 11 has been cancelled without prejudice or disclaimer. Applicants believe the Examiner is referring to the instant claim 14, not claim 13, in applying these grounds of rejection, since claim 13 depends from claim 12. Claim 14 has been cancelled without prejudice

or disclaimer as being directed to unelected subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

**c) 35 U.S.C. § 102(a)**

Claims 1, 2, 5, 8, 10, 11, 12, 13, 16, 17, 20 and 21 stand rejected as anticipated in view of Kim. Claim 6 has not been rejected as anticipated by Kim. Without conceding the correctness of the Examiner's position or the need for amendment, claim 1 has been amended to incorporate the limitation found in now cancelled claim 6. Kim therefore cannot anticipate amended claim 1. Claims 2, 5, 8, 10, 12, 13, 16, 17, 20 and 21 depend directly or indirectly from claim 1 and therefore cannot be anticipated by Kim. Claim 11 has been cancelled without prejudice or disclaimer. Reconsideration and withdrawal of this rejection is respectfully requested.

**d) 35 U.S.C. § 103(a)**

Claims 1-4, 6, 7, 9-13, 16, 17, 20 and 21 stand rejected as obvious over Rhee et al. in view of Schmolka et al. The Examiner contends that Rhee et al. discloses a conjugate of a glycosaminoglycan and a synthetic polymer, preferably an activated polyethylene glycol or derivative thereof having a molecular weight of 1,500-20,000. The Examiner further states that the glycosaminoglycan can be hyaluronic acid with from 1-5,000 disaccharide subunits or a molecular weight of about 380-1,900,000, with the synthetic polymer being a PEO-PPO block copolymer. The Examiner further states that these conjugates can be used as a component in various pharmaceutical compositions including compositions for injection. The Examiner concludes that the gel prepared by Rhee is reasonably considered to be useful in the treatment of

joint disease or assisting or treating surgical operations or repairing tissues even while acknowledging that Rhee neither discloses a conjugate in which the synthetic copolymer is PEO-PPO-PEO or PPO-PEO-PPO, nor discloses a hyaluronic acid component of the polymer having a molecular weight of 1,500,000. The Examiner further contends that Schmolka discloses several EPO-PPO copolymers having the structure PEO-PPO-PEO or PPO-PEO-PPO. The Examiner contends that it would have been obvious to use the triblock copolymers disclosed by Schmolka et al. and a hyaluronic acid with a molecular weight of less than 1,500,000, because Rhee et al. discloses that PEO-PPO copolymers generally are useful in the disclosed conjugates and because Rhee et al. discloses a range of molecular weights (380-1,900,000) which overlap the claimed range of under 1,500,000. Applicants respectfully traverse.

Regarding a combination of Rhee et al. and Schmolka et al., the hyaluronic acid modification product of the present invention undergoes sol-gel phase transition in the range between 20°C and 35°C, while Rhee et al. does not teach or suggest such a hyaluronic acid modification. Rhee et al. does not teach or suggest any parameter which induces the sol-gel phase transition. In view of the teaching that “the conjugates contain large amounts of water when formed” or “the solid implants or particles rehydrate and expand in size approximately three- to five-fold” described in the last 9 lines of Abstract in Rhee et al., a person skilled in the art could not have conceived the feature of the present invention (*i.e.*, an improvement of storativity by viscosity increase with phase transition), because if the conjugates having the high expansibility of Rhee et al. were administered into a joint, they would cause the patient to suffer pain and also cause

damage to the patient's joint. Further, this is proof that the conjugates of Rhee et al. are not applicable for the purposes as claimed in claims 1-4, 6, 7, 9-13, 17, 20 and 21. Thus, the Examiner has not set forth a *prima facie* argument for obviousness.

Thus, it is believed that it would not have been obvious for a skilled person to arrive at the present invention based on the teachings of Rhee et al. alone, or in combination with the teachings of Schmolka et al. which only disclose the existence of PEO-PPO copolymer.

Claims 1-4, 7-13, 16, 17, 20 and 21 stand rejected as obvious over Spaltro et al. in view of Schmolka et al. The Examiner contends that Spaltro et al. disclose block copolymers containing a polysaccharide moiety and a polyalkylene oxide moiety with hyaluronic acid listed as a suitable polysaccharide with a molecular weight of 1,000-50,000. The Examiner further states that polyalkylene oxides include copolymers of ethylene oxide and propylene oxide with the polymer being endcapped, leading to a product of formula AB with A being a polysaccharide and B being a polyalkylene oxide where the polymer is attached to hyaluronic acid at only one end. The Examiner also contends that the block polymers described by Spaltro et al. are used in pharmaceutical formulations and are useful for treating joint diseases or assisting or treating surgical operations or repairing tissue. The Examiner acknowledges that Spaltro et al. does not exemplify a block polymer in which hyaluronic acid is less than 1,500 kD or less than 5 kD, or one in which the polyalkylene oxide is PEO-PPO-PEO or PPO-PEO-PPO having a molecular weight of 1,200 daltons or more. The Examiner contends that Schmolka et al., though, discloses several PEO-PPO copolymers having the structure PEO-PPO-PEO or PPO-PEO-PPO. The Examiner

concludes that it would have been obvious to practice the claimed invention with the triblock copolymers disclosed by Schmolka et al. and a hyaluronic acid with a molecular weight of less than 5,000 because Spaltro et al. discloses that PEO-PPO copolymers generally are useful in the disclosed conjugates, and because Spaltro et al. discloses a range of molecular weights (1,000-50,000) that substantially overlaps the claimed range of under 1500000 or under 5000, and because the disclosed range of 1,000-20,000 for the polyalkylene oxide substantially overlaps the claimed range of 1,200 or more. Applicants respectfully traverse.

Without conceding the correctness of the Examiner's position or the need for amendment, claim 1 has been amended to include the limitation found in the now cancelled claim 6. Claim 6 was not rejected over Spaltro et al. in view of Schmolka et al., and therefore amended claim 1 is not obvious. Claims 2, 3, 4, 7, 8, 9, 10, 12, 13, 16, 17, 20 and 21 all depend directly or indirectly from claim 1 and, therefore, are also not obvious. Claim 11 was cancelled without prejudice or disclaimer. Reconsideration and withdrawal of this rejection is respectfully requested.

e) **Non-Statutory Obviousness-Type Double Patenting**

Claims 1, 3-5, 10-13, 16, 17, 20 and 21 stand rejected on the grounds of non-statutory obviousness-type double patenting as being obvious over claims 1-7 and 15 of copending U.S. Application No. 10/571,005. Applicants respectfully traverse.

Without conceding the correctness of the Examiner's position or the need for amendment, claim 1 has been amended to incorporate the limitation from now cancelled claim 6. Claim 6 was not found obvious over 10/571,005, therefore, amended claim 1 is not obvious. Claims 3-5, 10, 12,

13, 16, 17, 20 and 21 all depend directly or indirectly from amended claim 1 and so are also not obvious. Claim 11 has been cancelled without prejudice or disclaimer. Reconsideration and withdrawal of this rejection is respectfully requested.

**CONCLUSION**

In view of the foregoing amendments and remarks, applicant believes the pending application is in condition for allowance, and earnestly solicits same.

If fees in addition to those transmitted herewith are required for the filing of this amendment, the Commissioner is hereby authorized and requested to charge any such fees, up to a maximum of \$300, to Darby and Darby Deposit Account No. 04-0100.

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Respectfully submitted,

By   
Louis J. DelJuice

Registration No.: 47,522  
DARBY & DARBY P.C.  
P.O. Box 770  
Church Street Station  
New York, New York 10008-0770  
(212) 527-7700  
(212) 527-7701 (Fax)  
Attorneys/Agents For Applicant